

Role of Bioactive Food Components in Cancer: Challenges in Interpreting Human Studies

Cheryl L. Rock, PhD, RD

Dept. of Family and Preventive Medicine

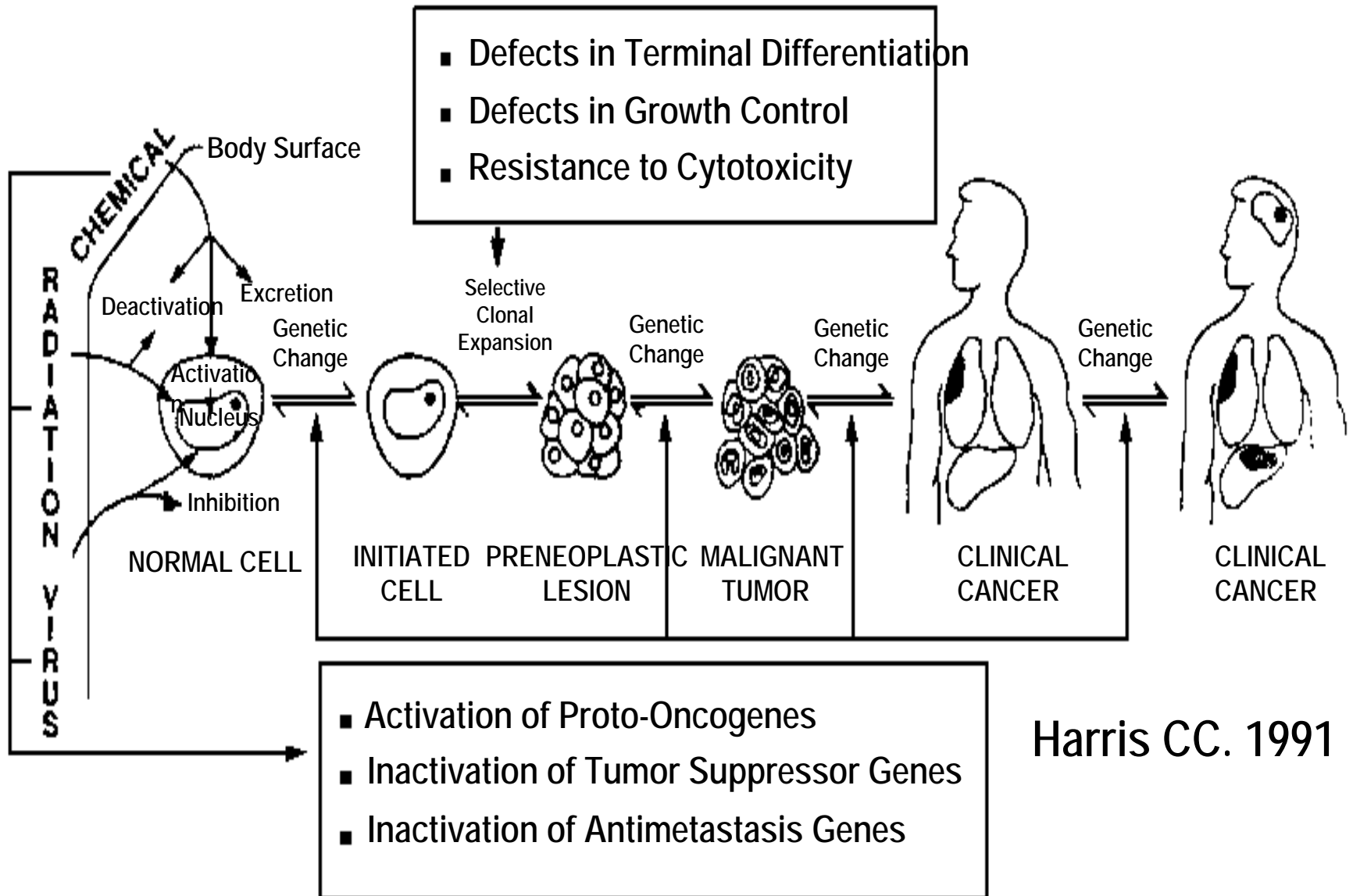
Cancer Prevention and Control Program

University of California, San Diego

Initiation

Promotion Conversion

Progression



Harris CC. 1991

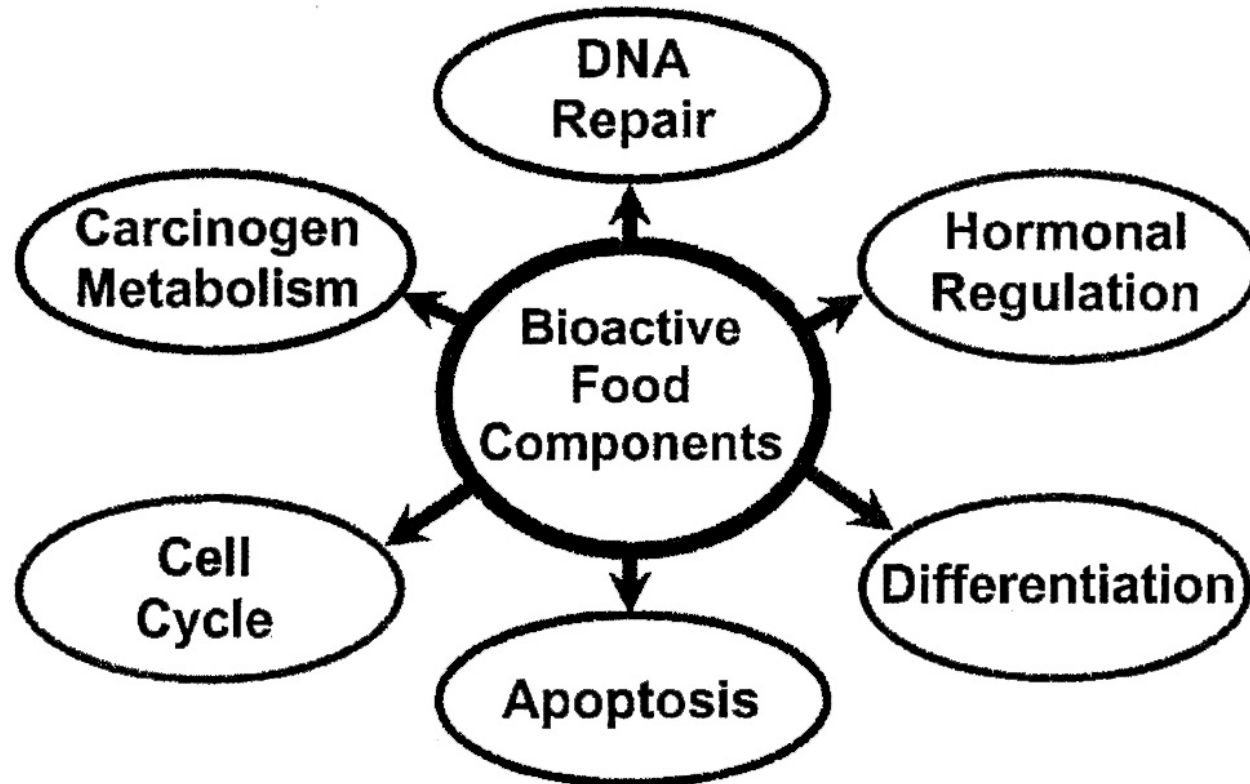
Bioactive Food Components and Cancer Risk and Progression

- Nutrients: Vitamins, minerals
- Carotenoids
- Flavonoids
- Organosulfur compounds
- Isothiocyanates
- Indoles
- Monoterpenes
- Phenolic acids

Proposed Mechanisms

- Antioxidant activity
- Effects on cell proliferation, differentiation, and apoptosis
- Enzyme induction or inhibition and detoxification
- Effects on immune function
- Effects on angiogenesis, and cell adhesion and invasion
- Regulation of hormone metabolism
- Antibacterial and antiviral effects

Diet May Influence Genetic & Epigenetic Events Associated with Several Cancer Processes



Milner JA. J Nutr 2004; 134:2492S.



Problems with the Traditional Approach

- Isolated food components
 - Potential synergy and context of consumption
 - Formulation
- Animal models
 - Differential uptake and metabolism
- Cell culture studies
 - Context of intact biological system
 - Differential cell functions and carcinogenic process

Overall Dietary Pattern?

- Inconsistencies across types of cancer and various populations that have been examined
- Consuming vegetables, fruit, whole grains, lean meats or meat alternates, and low fat dairy foods has been associated with lower risk for mortality and reduced risk for many cancers

Observational Study Challenges

- Cancer etiology is multifactorial
- Influence of genetic susceptibility on response to exposure is important to address
- Depending on the polymorphism or other characteristic, the size of the sample needed for sufficient statistical power may be an important limitation

Limitations in Diet Assessment

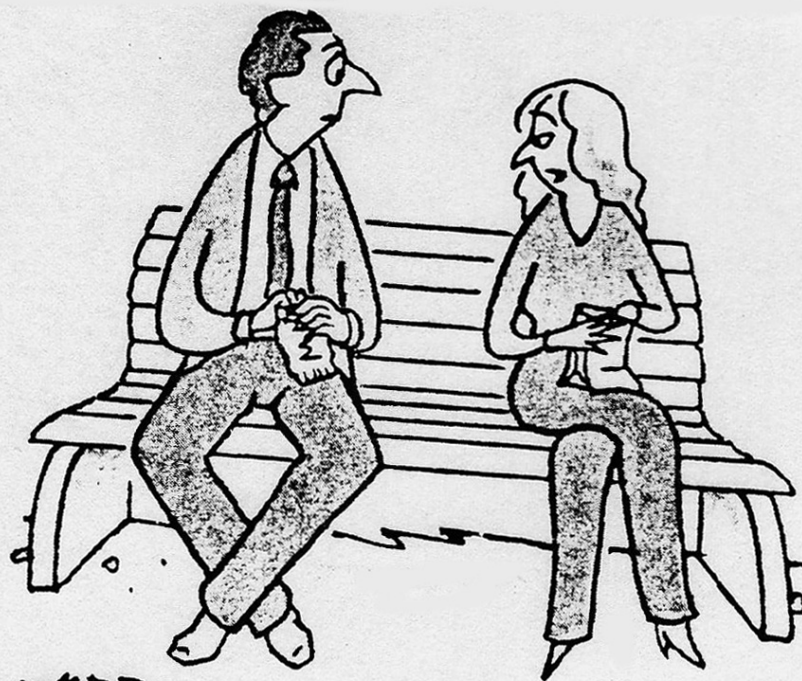
- Established limitations in accuracy
- Variability in food content
- Characteristics relating to context of consumption are difficult to examine

Calibration vs. Validation

- Without biological markers of diet, self-reported dietary data reflect a considerable amount of bias, inaccuracy, and error
- There is no gold standard
- Similar errors correlate across different methodologies of diet assessment

Bioactive Food Components in Human Studies

- Food content data for phytochemicals and dietary constituents of interest are often based on limited quantity and quality of assays, which particularly constrains assessment of intake
- Food and eating patterns are complex and multi-component by nature
- Categorizations are inconsistent



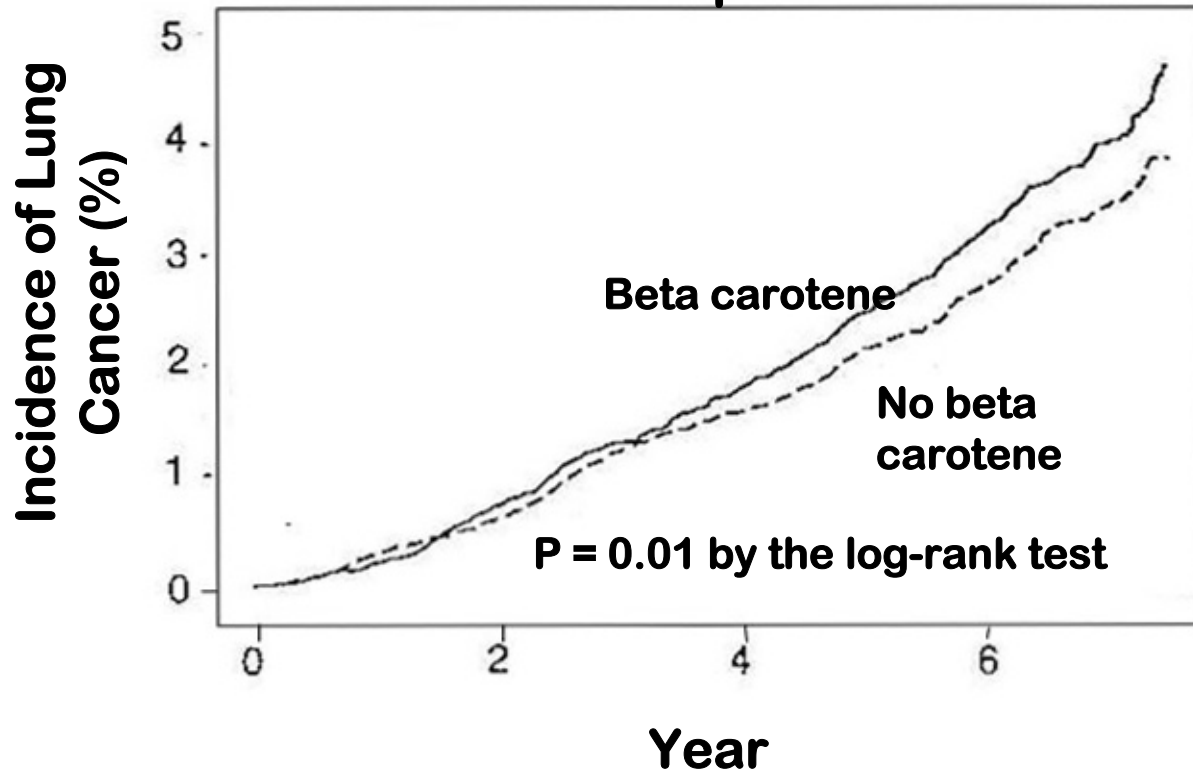
WARP

"When your mother told you to eat something green every day, I don't think she had M & M's in mind."

Example: Beta-Carotene Supplement Trials

- Consistent associations between dietary intake, circulating beta-carotene concentration, and risk for lung cancer
- Limited knowledge of metabolism and other key characteristics
- Trials found increased, rather than decreased, risk for lung cancer, and detrimental effects at high doses

Kaplan-Meier Curves for the Cumulative Incidence of Lung Cancer Among Participants



ATBC Study Group 1994

Example: Dietary Isoflavones and Phytoestrogens

- Soy foods (tofu, soy milk) vs. hidden sources of soy (foods containing added soy protein isolate, soy concentrate or soy flour)
- Soy foods explained only 16% of the variance in total isoflavonoid excretion, with the latter associated with processed and high-fat meat intake (Lampe et al. 1999)
- Foods with soy additives (doughnuts and white bread), and frequently-consumed foods with low amounts (orange juice, coffee) are major sources of phytoestrogenic compounds (Horn-Ross et al., 2000)

Large Intervention Study Challenges

- Practical aspects of collecting biological samples from free-living subjects at several clinic sites
- Methods for biomarker analysis must be usable with stored samples
- Genetic studies increase the complexity of working with IRBs

Recommendations

- Timing may be crucial in interpretation
- Target population should be well-characterized, especially relating to genetic factors
- Research questions and conclusions should be appropriately based on a study design that can address the questions and support the conclusions
- Develop and use biomarkers in observational and intervention studies

Biomarkers in Nutrition Research

- Biological indicators of dietary intake
- Indicators of biological or cellular activity of dietary constituents, although the activity may not be the primary mechanism
- Molecular or cellular markers that predict disease risk or biological process (surrogate endpoint biomarkers)

Example: The Women's Healthy Eating and Living (WHEL) Study

- Purpose: In a randomized trial, to test whether a diet rich in vegetables, fruit and fiber, and low in fat, is associated with a longer breast cancer event-free interval in breast cancer survivors
- Subjects: Women (3088) diagnosed with Stage I, II, or IIIA invasive breast cancer within the previous 48 months, following initial treatments



Change from Baseline at 12 Mo: Vegetables

(N = 2970, intent to treat analysis)

	Baseline	Intervention	Comparison
Vegetables	3.9 ± 0.04	+3.2 (+3.0, +3.4)	+0.0 (-0.1, +0.1)
Green vegetables	0.7 ± 0.01	+0.4 (+0.4, +0.5)	+0.1 (+0.0, +0.1)
Orange vegetables	0.4 ± 0.01	+0.3 (+0.3, +0.4)	+0.0 (-0.0, +0.1)
Tomato	0.6 ± 0.01	+0.2 (+0.2, +0.2)	+0.0 (+0.0, +0.1)
Cruciferous g/d	31.4 ± 0.70	+15.5 (+12.6, +18.5)	-1.5 (-3.7, +0.8)
Veg. juice mL/d	15 ± 10	+232 (+221, +242)	-3 (-6, +1)

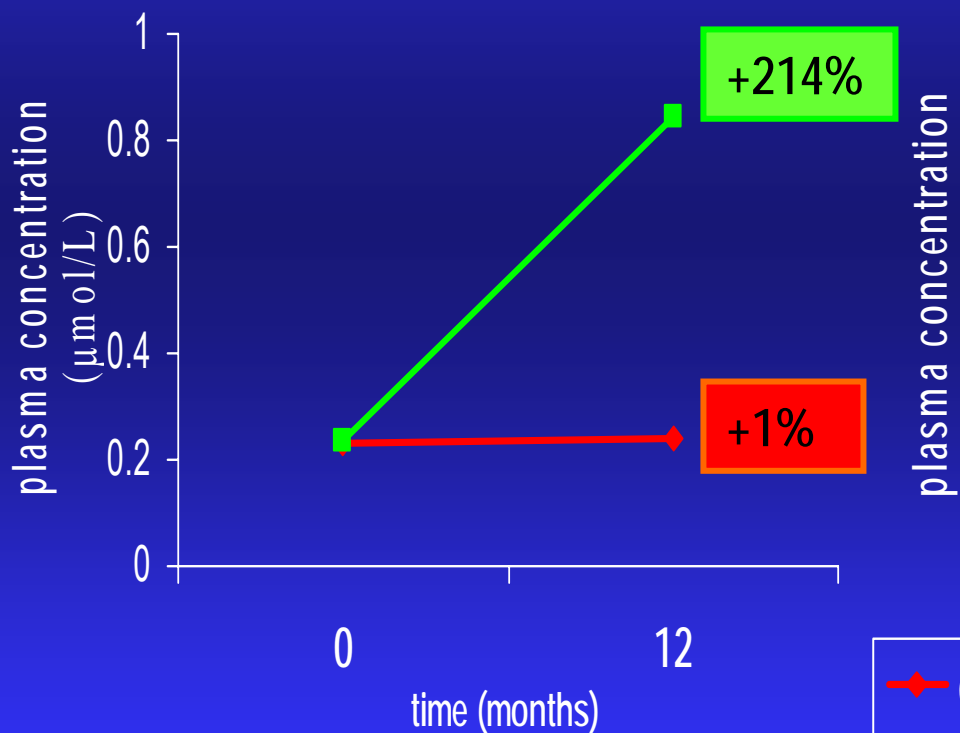
Vegetables in servings/day, vegetable juice in mL/day

Cruciferous vegetables in g/day

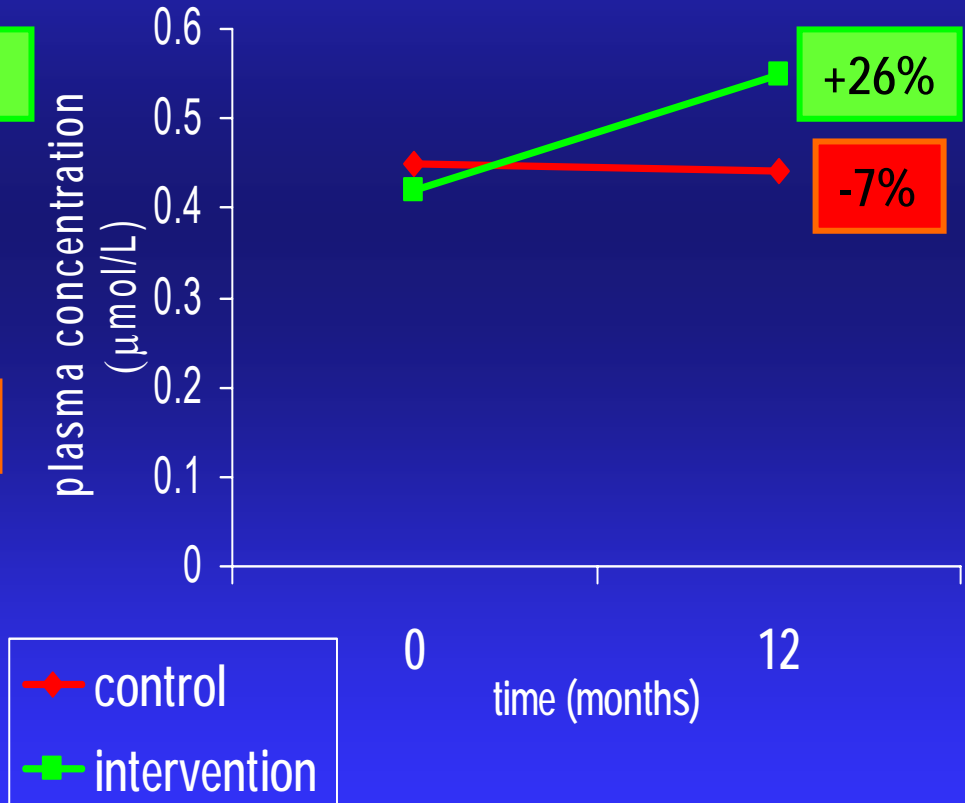
WHEL Study

Change in Circulating Carotenoid Concentrations

a-Carotene



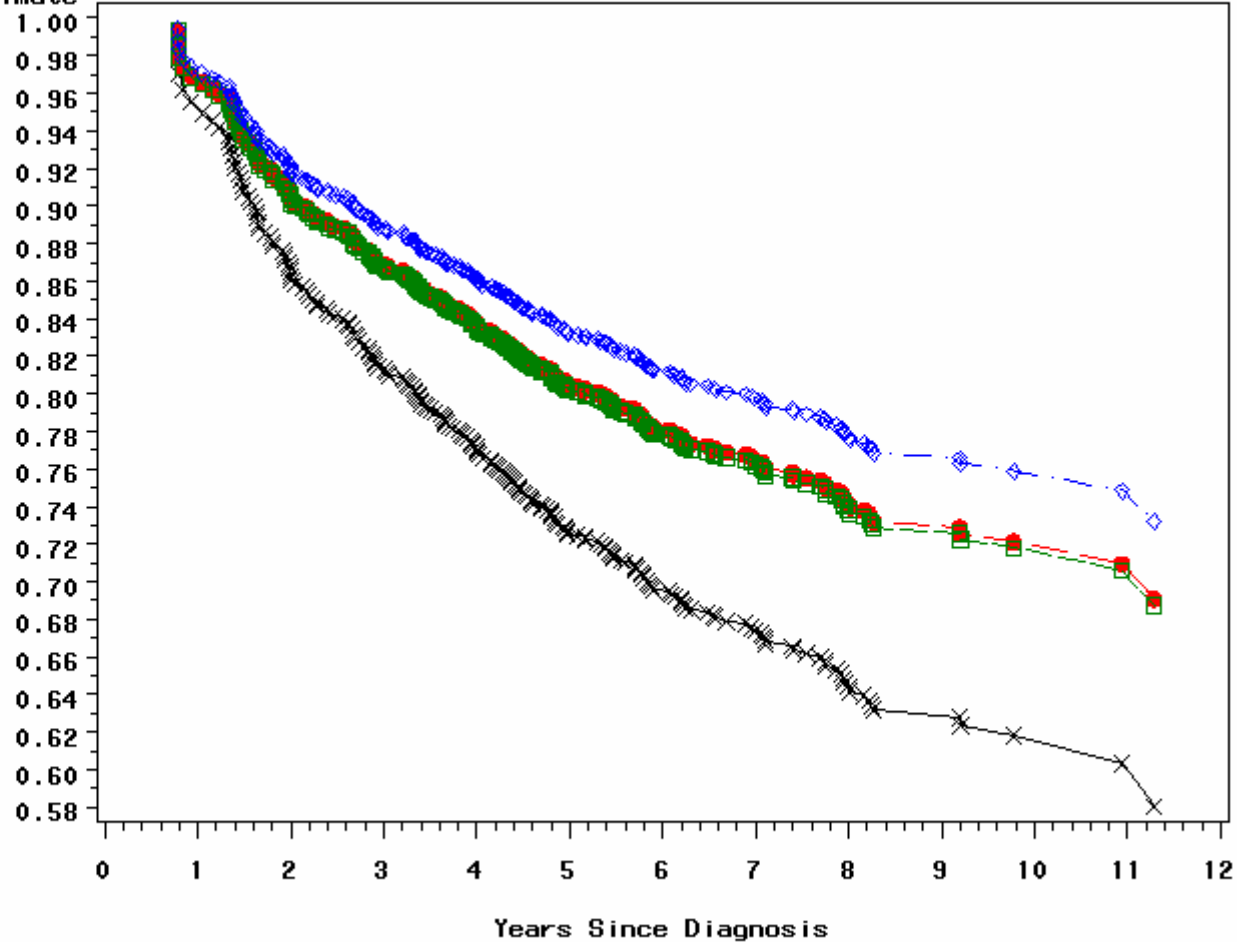
Lutein



Other Biomarkers

- Urinary 8-hydroxy-2'-deoxyguanosine (8OHdG) and 8-isoprostaglandin $F_{2\text{-}\alpha}$ (8-iso-PGF_{2 α}) in first morning void samples in one subset
- Urinary isothiocyanates and dithiocarbamates in first morning void samples in another subset

Survivor Function Estimate



Baseline Total Carotenoid Quartile

x x x 1

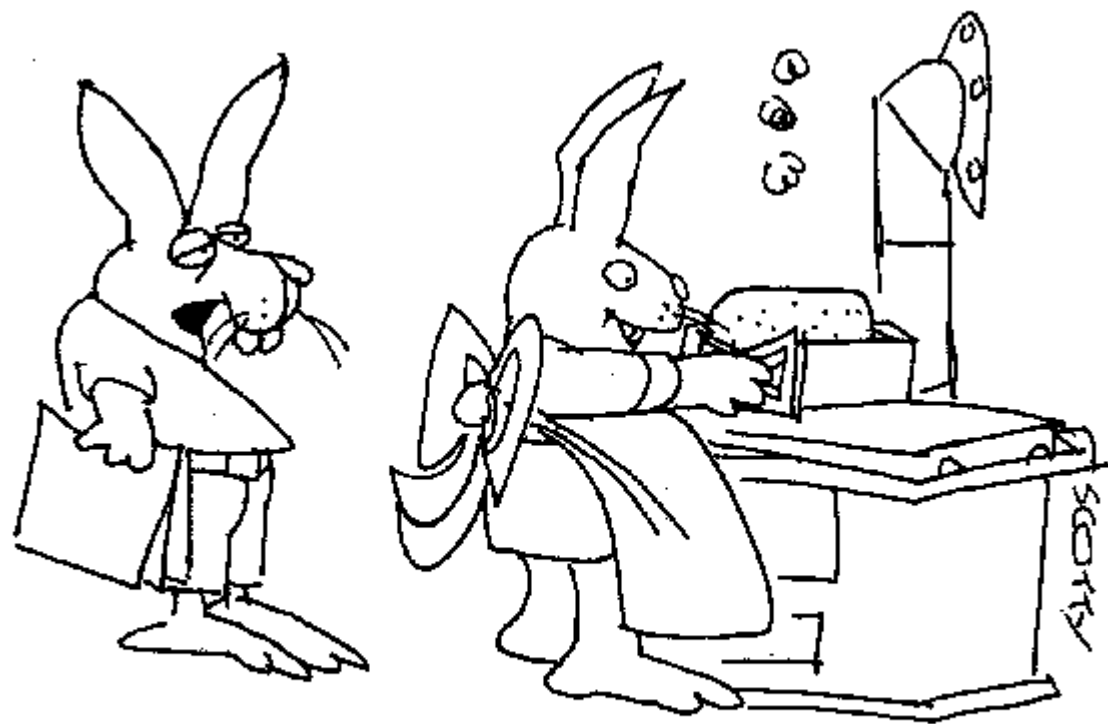
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Future Research Directions

- Development and use of biomarkers in human research relating bioactive food components to cancer
- Measurement and characterization of influencing factors: Genetic factors and contextual influences
- Improved approaches to describing dietary intakes and interpretation of these data



"Not another carrot cake!"